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CARDIOMYOCYTE CELLULAR REGULATION ON EXERCISE

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ABSTRACT

85% of deaths from cardiovascular disease are caused by CHD. More than 75% of deaths from cardiovascular disease occur in low- and middle-income countries. Myocardial injury caused by ischemia-reperfusion (IR) is a serious clinical problem. Reperfusion injury can cause damage or death to the myocardium and coronary vessel endothelium. Therefore it is necessary to develop a strategy of cardiac regeneration, both for the prevention and curative of cardiovascular disease. Cellular reprogramming occurs in cardiomyocytes in response to physical exercise. Cardiomyocytes keep up with increased demand, reflecting that there is optimal energy potential and reserve capacity. It is often referred to as the "athlete's heart". Cardiac remodeling in response to chronic exercise to match the increased workload is by increasing heart size, in the absence of cardiomyocyte proliferation. This physiological growth is accompanied by an increase in energy production capacity, especially in mitochondria. Normal hypertrophic growth is characterized by normal contractile function at rest. This is in contrast to the pathological growth produced by prolonged hypertension or ischemic heart disease, in which contractile function and metabolic energy production are decreased. At the cellular and molecular level, it is clear that the activation of signaling pathways and the resulting transcriptional response different between physiological and pathological cardiac growth.

Keywords : myocardial injury; cardiomyocytes regeneration; athlete's heart; cardiac biomolecular; physical exercise

INTRODUCTION

Elaborate myocardial infarction (IM) is a serious health problem, because the heart's regeneration ability is very limited in adult human hearts. Various efforts in all aspects of health need to be researched and developed to overcome problems that have not been completed this decade, including knowing the effects of physical exercise doses on cardiac regeneration. The potential for heart regeneration in adult humans is very small, but it is possible for researchers to continue to develop science and technology in the field of heart regeneration, especially exercise.

METHODS

This literature study was obtained by searching scientific research articles using Frontiers, Nature, and Mendeley in electronic form from a virtual library. This type of research uses a literature review method sourced from journals and publications of preliminary studies related to strategy in the field of cardiac regeneration, both for the prevention and curative of cardiovascular disease. The keywords used for the search are myocardial injury; cardiomyocytes regeneration; athlete's heart; cardiac biomolecular; /physical exercise. and using Indonesia or English language. Libraries that are not available full text will

be excluded. The review are limited by the year of publication and the accessible of the search engine.

RESULTS AND DISCUSSION

During exercise, the heart is subjected to intermittent hemodynamic stress from pressure overload, volume overload, or both. Cardiac hypertrophy occurs to normalize wall tension according to LaPlace's law. Conventionally, pressure overload results in concentric hypertrophy (increase in LV thickness and cardiomyocyte dilation), while volume excess results in eccentric hypertrophy (increase in LV radius and cardiomyocyte length) (Pitoulis et al., 2022). To normalize this stress and to meet the systemic demands that will result in an increase in blood supply, the heart undergoes morphological adaptations to repeated exercises with an increase in muscle mass, especially through an increase in the thickness of the walls of the ventricular chambers (Lavie et al., 2015; Nystoriak & Bhatnagar, 2018). This increase in heart size is primarily the result of an increase in cardiac myocyte size. Adaptive remodeling of the heart in response to exercise usually results in a maintenance or improvement of contractile function. This is in contrast to pathological remodeling due to sustained pressure overload (eg, during hypertension or aortic stenosis), which can progress to loss of contractile function and heart failure (Nystoriak & Bhatnagar, 2018).

Exercise can increase left ventricular contractile and myocardial oxygen consumption 3 to 10 times above resting levels. The increase in myocardial oxygen consumption is due to the increased concentration of ADP, which triggers oxidative phosphorylation to regenerate ATP at a higher rate. Changes in cardiac substrate catabolism in providing fuel for increased energy demands depend on several integrated factors including workload, circulating hormones, and substrate availability and abundance (Gibb & Hill, 2018). Cardiac myocytes can keep up with increased demand, reflecting that there is optimal energy potential and reserve capacity. It is often referred to as the "athlete's heart". Cardiac remodeling in response to chronic exercise to match the increased workload is by increasing heart size, in the absence of cardiac myocyte proliferation. This physiological growth is accompanied by an increase in energy production capacity, especially in mitochondria. Normal hypertrophic growth is characterized by normal contractile function at rest. This is in contrast to the pathological growth produced by prolonged hypertension or ischemic heart disease, in which contractile function and metabolic energy production are decreased. At the cellular and molecular level, it is clear that the activation of signaling pathways and the resulting transcriptional response will differ between physiological and pathological cardiac growth (Vega et al., 2017).

Cellular reprogramming can occur in cardiomyocytes in response to physical exercise. Activation of ErbB2-4-like receptor tyrosine kinases (RTKs) via growth factors (eg, insulin-like growth factor 1 (IGF-1) or Neuregulin-1) increases the phosphatidylinositol 3 phosphate kinase (PI3K), protein kinase B (Akt), mammalian target of rapamycin (mTOR), glycogen synthase kinase 3 β (GSK3 β) that leads to proliferation, physiological hypertrophy and cardiac repair mechanisms in response to injury. Activation of beta 3-adrenergic receptors (β3-AR) will increase endothelial nitric oxide synthase (eNOS) and followed by an increase in intracellular nitric oxide (NO) which will increase contractility and reduce pathological fibrosis or hypertrophy. Changes in miR expression can affect intracellular signaling pathways (including Akt and eNOS); mediates apoptosis and the cell development cycle; affect cardiac function and fibrosis through changes in collagen production and matrix metalloproteinase (MMP) expression. Exercise induces mitochondrial renewal and decreased apoptosis through changes in the ratio of B-cell lymphoma 2 (Bcl-2)/ Bcl-2-associated X protein (Bax). Activation of adenosine monophosphate-activated protein kinase (AMPK) overcomes pathological hypertrophy and reduces profibrotic remodeling. Paracrine secretion from extracellular vesicles containing miR is an intermediate in reducing I/R injury and cellular apoptosis (Schüttler et al., 2019).

Exercise-induced cardiac hypertrophy is associated with increased mitochondrial biogenesis in various animal models. Recent studies have shown that physiological cardiac hypertrophy induced by swimming training in rats is associated with increases in mitochondrial respiration-supported palmitoyl carnitine and ATP production rates in cardiac muscle fiber permeability (Abel & Doenst, 2011). Signaling pathways that can affect mitochondrial function in physiological and pathological cardiac hypertrophy (Fig. 2.18). In physiological cardiac hypertrophy, which occurs in response to exercise, there is an increased activation of class 1A PI3Kα, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and AMPK, where these factors can increase mitochondrial biogenesis and increase the capacity mitochondrial oxidation. Growth factors such as insulin receptor (IR) and IGF-1R may be required for mitochondrial adaptation to exercise-induced cardiac hypertrophy (Abel & Doenst, 2011).

The signaling mechanisms activated in the compensatory stage of pathological cardiac hypertrophy have been relatively poorly studied. AMPK activation will increase glucose uptake and glycolysis, although mitochondrial respiration capacity is relatively constant, and the level of Fatty Acid Oxidation (FAO) will decrease even though peroxisome proliferator activated receptor α (PPAR-α) is normal, then an allosteric regulatory mechanism occurs. Most studies report that there may be a decompensated phase of cardiac hypertrophy or LV dysfunction. At this stage, there are many disturbances in signaling pathways that can impair mitochondrial function, including decreased expression or activity of transcription regulators that regulate mitochondrial biogenesis and oxidative capacity (i.e. PGC-1α, and PPAR-α) and decreased mitochondrial DNA transcription. G-protein-coupled receptors activate class 1B PI3Kγ leading to constitutive activation of Akt, which can suppress mitochondrial function. HIF-1α activation causes increased FA uptake and PPARβ-mediated lipogenesis (Tyagi et al., 2011) which can increase lipotoxicity, which in turn can impair mitochondrial function. Reduced cardiolipin content and remodeling of the mitochondrial proteome also contribute to mitochondrial dysfunction. Mitochondrial dysfunction increases oxidative stress leading to a vicious cycle of progressive mitochondrial damage (Abel & Doenst, 2011).

Cellular communications within the heart must be coordinated to ensure that cellular crosstalk directs the appropriate biological response, and various cell types respond in a harmonious way to changing environmental factors to which the heart is exposed. Transcription factors can act as conductors, responding to external stimuli and paracrine messages from other cells, and changing the expression of paracrine and autocrine factors produced by the cell. One example of such a transcription factor is a factor induced by hypoxia, HIF1α. HIF1 levels will increase in response to hypoxia and ischemia, can alter the expression of various proteins including angiogenic factors, vasomotor tone-determining peptides, proteins that can alter endothelial adhesion characteristics, and which regulate glucose uptake and metabolism in cardiac myocytes, and even enhance survival cardiomyocyte life. Genes under transcriptional control by either HIF1α or HIF2α include all glycolytic enzymes, Glut1 glucose transporter, VEGF, PDGF-B, HGF, TGFβ1, iNOS, ET1, heme oxygenase, connective tissue growth factor (CTGF), and many others. Thus, HIF mediated by transcription factors coordinates diverse vascular and myocyte responses to ischemia (Tirziu et al., 2010).

Signaling molecules bind to extracellular or intracellular receptors to elicit specific cellular responses. Most signaling molecules are hydrophilic (eg, acetylcholine) and cannot cross cell membranes. Therefore, it needs receptors on the cell surface. Other signaling molecules are hydrophobic, such as steroid hormones, or small nonpolar molecules, such as NO, both of which have the ability to diffuse through the lipid bilayer. Ligands require the presence of intracellular receptors. Hydrophilic ligands have a very short lifetime (a few milliseconds to minutes at the most), whereas hydrophobic ligands last for a long period of time (a few hours to a few days). Signaling molecules often act together, so several different ligands are required before a specific cellular response can be elicited. Ligand combinations can elicit different

responses from different cells. For example, acetylcholine causes skeletal muscle cells to contract, but in cardiac muscle cells to relax, vascular endothelial cells to release NO, and parenchyma cells of some glands to release secretory granules. The binding of a ligand or signaling molecule to a receptor activates a system of intracellular second messengers, initiating a cascade of reactions that produce the required response. The receptor changes conformation, with activation of adenylate cyclase, a transmembrane protein in the cytoplasmic region that catalyzes the transformation of ATP to cAMP. cAMP is one of the most common second messengers. cAMP activates an enzyme cascade within the cell. Other second messengers include calcium (Ca2+), cGMP, inositol triphosphate (IP3), and diacylglycerol (DAG). The receptor-ligand complex activates gene expression, or transcription (formation of messenger ribonucleic acid (mRNA)). Transcription can be induced directly, producing a fast primary response, or indirectly, bringing about a slower secondary response. The protein mRNA codes necessary to activate gene expression (Gartner & HIatt, 2014).

CONCLUSION

The increase in heart size is mainly due to an increase in the size of cardiac myocytes. Adaptive remodeling of the heart in response to exercise usually results in maintenance or improvement of contractile function. This is in contrast to pathological remodeling due to sustained stress overload (eg, during hypertension or aortic stenosis), which can progress to loss of contractile function and heart failure. Exercise-induced cardiac hypertrophy is associated with increased mitochondrial biogenesis in various animal models. Cellular communications within the heart must be coordinated to ensure that cellular crosstalk directs the appropriate biological response, and various cell types respond in a harmonious way to changing environmental factors to which the heart is exposed by exercise

CONFLICT OF INTEREST

The authors declare no conflict of interest

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